Changes in cardiac repolarization caused by interferon therapy

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1 Introduction

A progression from viral myocarditis to dilated cardiomyopathy has been recently established [1] due to developments in the molecular analyses of autopsy and endomycardial biopsy using modern immunological techniques. Especially, the persistence of virus in the myocardium for a longer time can lead to chronic myocarditis and finally to dilated cardiomyopathy and destruction of cardiac muscle cells [2]. A new promising therapy of the virally induced myocarditis seems to be treatment with interferon. This therapy is known to augment the inflammatory response which can lead to virus elimination from the heart tissue. In the present study, patients with myocarditis and virus-positive biopsy have been treated by interferon and followed up using magetocardiographic (MCG) mapping. Based on our previous results [3] which established a strong correlation between the inflammation stage of myocardium and a new MCG parameter electrical Circulation (EC), we expect to observe changes in myocardial signal propagation during the interferon therapy. We intend to test, to what extent the MCG mapping allows us to non invasively monitor inflamed myocardium during the interferon therapy.

2 Methods

2.1 Spatio-temporal turbulence analysis

To study spatio-temporal beat-to-beat variability we applied the moving current dipole model in a half plane volume conductor providing the parameterization of an actual location and strength of the current source:

$$\vec{B} = \frac{\mu_0}{4\pi} \cdot \frac{\vec{J} \times \vec{R}}{\left|\vec{R}\right|^3} \tag{1}$$

where $\vec{B}$, $\vec{J}$ and $\vec{R}$ are the magnetic flux density, current dipole and location vector, respectively. The vectors $\vec{J}$ and $\vec{R}$ are calculated for every time point of a measurement. To compare different heart beats in time domain to each other, we have applied R-peak triggering. Thus, it is possible to calculate the mean values of $\vec{J}$ and $\vec{R}$ vectors and simultaneously to investigate the spatial distribution of $\vec{J}$ vectors for each time instant of the heart cycle separately. By means of scalar and vector products the current dipole vectors can be decomposed, relative to the mean location vector $\vec{R}_0(t)$, in two orthogonal components: tangential and radial. These two vector components form new variables: Source S and Circulation $\vec{C}$, defined as follows

$$S(t) = \frac{1}{N\sigma(\vec{R}_0(t))} \sum_{i=1}^{N} \vec{J}_i \cdot \vec{R}'_i \quad , \qquad \vec{R}'_i = \vec{R}_i - \vec{R}_0$$

$$\vec{C}(t) = \frac{1}{N\sigma(\vec{R}_0(t))} \sum_{i=1}^{N} \vec{J}_i \times \vec{R}'_i \tag{2}$$

where N and $\sigma(\vec{R}_0(t))$ are the number of heart beats (typically N=100) and the standard deviation of the location vector, respectively. The parameters Source and Circulation reflect the spatio-temporal beat-to-beat variability and describe the interdependence between the current dipole vectors and their locations [4,5]. Using analogy to the fluid flow Circulation describes rotation of the flow (vorticity) and Source, and represents flow directed radially to the origin (see Fig. 1).

2.2 Patients

9 Patients with a positive biopsy (DNA of adeno-virus) have been treated during many months of therapy with interferon α (1000 IE/3 days) and investigated magnetocardiographically every 2-4 weeks. MCG mapping has been carried out using a 49-channel gradiometer in a magnetically shielded room. A new parameter EC of Spatio-Temporal Turbulence Analysis describing beat to beat variability of electric signal propagation has been applied for about 100 consecutive heart beats. As a follow up parameter the EC value within the T-wave has been determined. A group of 5 healthy volunteers have been investigated additionally to determine the reproducibility of the analysis.

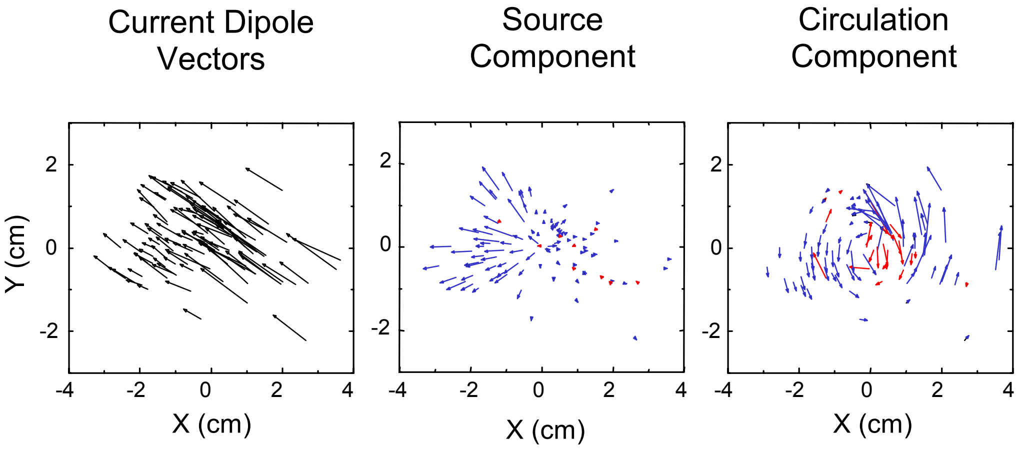

Figure 1: *Left: 2D projection of current dipole vector distribution obtained for about 100 consecutive heart beats at the maximum of the T-wave. Middle: Radial (Source) component of the same current dipole distribution. Right: Tangential (Circulation) component of the same current dipole distribution. The origin of the coordinate system corresponds to the mean location for this instant.*

3 Results

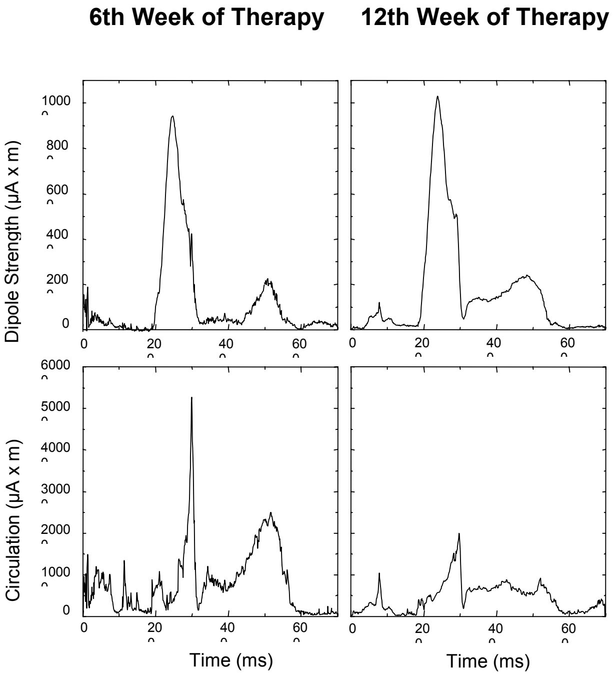

Figure 2: *Tracing of the mean current dipole (above) and electrical Circulation (below) over the entire heart cycle. In the tracing of the current dipole the P-wave, QRS-complex and T-wave can be seen. Left: A patient in the 6th week of the interferon therapy. Right: The same patient in the 12th therapy week. The normalized Circulation within the T-wave decreased from 12.0 to 4.0 .*

An example of the tracings of the current dipole vector and EC during the interferon therapy is presented in Fig. 2 . The changes within the T-wave can be observed clearly. As a follow up parameter, the EC within the T-wave, normalized on the amplitude of the current dipole vector, has been determined. In all patients an initial value of EC 3.3±3.0 increased after 5.4±3.0 weeks in average by a factor of 5.0 to the value 9.7±7.2 and decreased after 10.9±4.6 weeks by a factor of 4.7 to the value 3.0±1.9 . The reproducibility of EC values measured in healthy subjects was better than 15 %. Follow-ups in two different patients are depicted in Fig. 3 . In 6 patients a characteristic second increase of EC value has been seen.

4 Discussion

In all patients a strong increase followed by a similarly strong decrease of electric Circulation within the T-wave has been observed during the interferon therapy. This temporal dependence of electrical Circulation corresponds to the expected action of interferon and can be treated as a non invasive observation of the inflammation state of myocardium. The origin of a second increase in the T-wave Circulation observed in some patients during the interferon therapy is not clear. A comparison with results from other accompanying investigation, done in the frame of the present pilot study, with echo-cardiography or blood investigation is necessary. A final assessment of the interferon therapy is in progress.

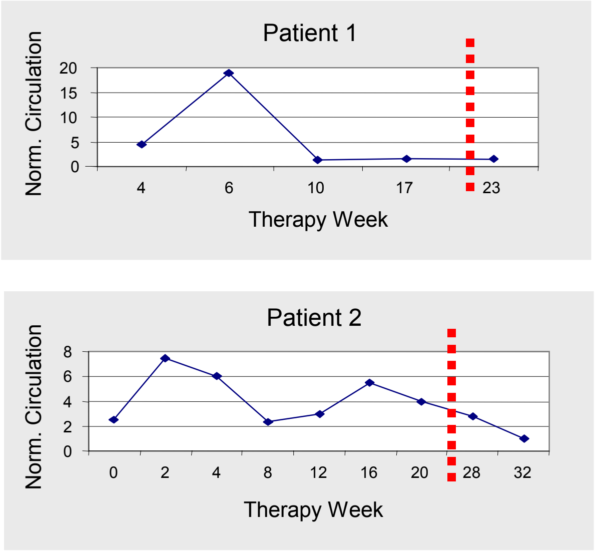

Figure 3: *Changes of the normalized Circulation in two different patients during the interferon therapy. The dashed red line shows the end point of the therapy.*

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References

1. C. Kawai, “From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future”, *Circulation*, **99**, 1091-1100, 1999.
2. M. Pauschinger, A. Doermer, U. Kuehl, P. Schwimbeck, W. Poler, R. Kandolf, and P.-H. Schultheiss, “Viral replication in the myocardium of patients with clinically suspected myocarditis”, *Circulation*, **99**, 889-895, 1999.
3. R. Agrawal, K. Czerski, P. Gödde, S Behrens, A. Morguet, U. Kuehl, and H.-P- Schultheiss, “Noninvasive Follow up of Myocarditis with Magnetocardiography”, *Med. & Biol. Eng. & Comp.*, **37**, 408-409, 1999.
4. L. Schmitz, K. Czerski, K. Brockmeier, R. Agrawal, U. Steinhoff, L. Trams, and M. Oeff, “Magnetocardiographic Turbulence Analysis in Patients with Long QT Syndrome”, *Journal of Electrocardiology*, **30**, 105-113, 1998.
5. K. Czerski, R. Agrawal, P. Gödde, S. Behrens, A. Morguet, and H.-P. Schultheiss, “Description of Electric Signal Propagation in Myocardium Using Analogy to Fluid Mechanics”, *Med. & Biol. Eng. & Comp.*, **37**, 412-414, 1999.